

## PATENT COOPERATION TREATY

23 AUG. 2005

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:

NSGENE A/S  
 Attn. NORGAARD, Jens Viktor  
 Baltorpvej 154  
 DK-2750 Ballerup  
 DENMARK

NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT AND  
 THE WRITTEN OPINION OF THE INTERNATIONAL  
 SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 23/08/2005	
Applicant's or agent's file reference 522-204-WO	<b>FOR FURTHER ACTION</b> See paragraphs 1 and 4 below
International application No. PCT/EP2005/051431	International filing date (day/month/year) 30/03/2005
Applicant NsGene A/S	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

**For more detailed instructions,** see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

**4. Reminders**


Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Müge Aydemir
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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  522 - 204 - WO	<b>FOR FURTHER ACTION</b>		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No.  PCT/EP2005/051431	International filing date <i>(day/month/year)</i>  30/03/2005	(Earliest) Priority Date <i>(day/month/year)</i>  30/03/2004	
Applicant  NsGene A/S			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2005/051431

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☒ in written format
- ☒ in computer readable form
- c. time of filing/furnishing
- ☒ contained in the international application as filed
- ☒ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2005/051431

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 89-108 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP2005/051431

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/475 C12N15/12 A61K38/18 A61K31/7088 A61K31/713  
 A61P25/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS, Sequence Search

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/39786 A (INNOGENETICS N.V; FRANSEN, LUCIA; DE BAETSELIER, PATRICK) 7 June 2001 (2001-06-07)  claims; figures; examples -----	1-76, 89-91, 104, 108-121
X	WO 01/57190 A (HYSEQ, INC; TANG, Y., TOM; LIU, CHENGHUA; DRMANAC, RADOJE, T; ASUNDI,) 9 August 2001 (2001-08-09)  page 59 - page 61; claims; examples; tables 2-6; sequences 1401,3369,417,2385 -/--	1-76, 89-91, 104, 108-121

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

5 July 2005

Date of mailing of the international search report

23 AUG 2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Madruga, J

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>-&amp; DATABASE Geneseq [Online] 6 November 2001 (2001-11-06), "Human protein SEQ ID NO 1401." XP002334619 retrieved from EBI accession no. GSN:AAM78739 Database accession no. AAM78739 SEQUENCE INFORMATION the whole document</p> <p>-&amp; DATABASE Geneseq [Online] 6 November 2001 (2001-11-06), "Human protein SEQ ID NO 3369." XP002334620 retrieved from EBI accession no. GSN:AAM79723 Database accession no. AAM79723 SEQUENCE INFORMATION the whole document</p> <p>-----</p> <p>WO 01/54474 A (HUMAN GENOME SCIENCES, INC; ROSEN, CRAIG, A; BARASH, STEVEN, C; RUBEN,) 2 August 2001 (2001-08-02)</p> <p>claims; sequences 675,845,255,425 -&amp; WO 01/55440 A (HUMAN GENOME SCIENCES, INC; ROSEN, CRAIG, A; BARASH, STEVEN, C; RUBEN,) 2 August 2001 (2001-08-02) paragraph [0638] - paragraph [0655]; claims; sequences 675,845,255,425 -&amp; DATABASE Geneseq [Online] 10 January 2002 (2002-01-10), "Human cDNA SEQ ID NO: 675." XP002334621 retrieved from EBI accession no. GSN:ABB10367 Database accession no. ABB10367 SEQUENCE INFORMATION the whole document</p> <p>-&amp; DATABASE Geneseq [Online] 10 January 2002 (2002-01-10), "Human cDNA SEQ ID NO: 845." XP002334622 retrieved from EBI accession no. GSN:ABB10537 Database accession no. ABB10537 SEQUENCE INFORMATION the whole document</p> <p>-&amp; DATABASE Geneseq [Online] 10 January 2002 (2002-01-10), "Human cDNA SEQ ID NO: 255." XP002334623 retrieved from EBI accession no. GSN:ABA06589 Database accession no. ABA06589 SEQUENCE INFORMATION the whole document</p> <p style="text-align: center;">-/--</p>	<p>1-76, 89-91, 104, 108-121</p>

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>-&amp; DATABASE Geneseq [Online]  10 January 2002 (2002-01-10), "Human cDNA  SEQ ID NO: 425."  XP002334624  retrieved from EBI accession no.  GSN:ABA06759  Database accession no. ABA06759  SEQUENCE INFORMATION  the whole document</p> <p>-----</p> <p>WO 01/83510 A (HUMAN GENOME SCIENCES, INC;  KOMATSULIS, GEORGE; RUBEN, STEVEN, M;  ROS) 8 November 2001 (2001-11-08)</p> <p>page 49 - page 51; claims; sequences  31,93,94  page 213 - page 225  page 245 - page 253  -&amp; DATABASE Geneseq [Online]  15 March 2002 (2002-03-15), "Human  secreted protein encoding polypeptide SEQ  ID NO 93."  XP002334625  retrieved from EBI accession no.  GSN:ABB57447  Database accession no. ABB57447  SEQUENCE INFORMATION  the whole document</p>	<p>1-76,  89-91,  104,  108-121</p>
P,X	<p>-----</p> <p>NISHINO JINSUKE ET AL: "Meteorin: a  secreted protein that regulates glial cell  differentiation and promotes axonal  extension"  EMBO (EUROPEAN MOLECULAR BIOLOGY  ORGANIZATION) JOURNAL,  vol. 23, no. 9, 5 May 2004 (2004-05-05),  pages 1998-2008, XP002334608  ISSN: 0261-4189  cited in the application  the whole document</p>	<p>1-121</p>
P,X	<p>-----</p> <p>WO 2004/035732 A (FIVE PRIME THERAPEUTICS,  INC; WILLIAMS, LEWIS, T; CHU, KETING; LEE,  ER) 29 April 2004 (2004-04-29)</p> <p>paragraph [0140] - paragraph [0147];  claims; sequence 91</p> <p style="text-align: center;">-/--</p>	<p>1-76,  89-91,  104,  108-121</p>



## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>-&amp; DATABASE Geneseq [Online] 12 August 2004 (2004-08-12), "Human secreted protein SEQ ID #91." XP002334626 retrieved from EBI accession no. GSN:ADP29324 Database accession no. ADP29324 SEQUENCE INFORMATION the whole document -----</p>	
A	<p>DATABASE EMBL [Online] 21 December 2001 (2001-12-21), "2023-57 Mouse E14.5 retina lambda ZAP II Library Mus musculus cDNA, mRNA sequence." XP002334627 retrieved from EBI accession no. EM_PRO:BG806341 Database accession no. BG806341 the whole document</p>	
A	<p>-&amp; MU X ET AL: "Gene expression in the developing mouse retina by EST sequencing and microarray analysis." NUCLEIC ACIDS RESEARCH. 15 DEC 2001, vol. 29, no. 24, 15 December 2001 (2001-12-15), pages 4983-4993, XP002334609 ISSN: 1362-4962 the whole document -----</p>	

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/051431

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Information on patent family members

International Application No

PCT/EP2005/051431

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/051431

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/051431

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# PATENT COOPERATION TREATY

**DUE DATE**

From the  
INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/EP2005/051431

International filing date (day/month/year)  
30.03.2005

Priority date (day/month/year)  
30.03.2004

International Patent Classification (IPC) or both national classification and IPC  
C07K14/475, C12N15/12, A61K38/18, A61K31/7088, A61K31/713, A61P25/00, A61P37/00

Applicant  
NsGene AS

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk - Pays Bas  
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Authorized Officer

Madrugá, J

Telephone No. +31 70 340-3121



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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
☒ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material:  
☒ in written format  
☒ in computer readable form
  - c. time of filing/furnishing:  
☒ contained in the international application as filed.  
☒ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 89-108 in respect of industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 89-108 in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☒ See separate sheet for further details



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2005/051431

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**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	77-88, 92-103, 105-107
	No: Claims	1-76, 89-91, 104, 109-121
Inventive step (IS)	Yes: Claims	77-88, 92-103, 105-107
	No: Claims	1-76, 89-91, 104, 109-121
Industrial applicability (IA)	Yes: Claims	1-88, 109-121
	No: Claims	

2. Citations and explanations

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 89-108 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**V. Reasoned statement with regard to novelty, inventive step or industrial applicability.**

**1. CITATIONS**

1.1 Reference is made to the following documents:

- D1: WO 01/39786 A (INNOGENETICS N.V; FRANSEN, LUCIA; DE BAETSELIER, PATRICK) 7 June 2001 (2001-06-07)
- D2: WO 01/57190 A (HYSEQ, INC; TANG, Y., TOM; LIU, CHENGHUA; DRMANAC, RADOJE, T; ASUNDI,) 9 August 2001 (2001-08-09)
- D3: WO 01/54474 A (HUMAN GENOME SCIENCES, INC; ROSEN, CRAIG, A; BARASH, STEVEN, C; RUBEN,) 2 August 2001 (2001-08-02)
- D4: WO 01/83510 A (HUMAN GENOME SCIENCES, INC; KOMATSOSULIS, GEORGE; RUBEN, STEVEN, M; ROS) 8 November 2001 (2001-11-08)
- D5: NISHINO JINSUKE ET AL: "Meteorin: a secreted protein that regulates glial cell differentiation and promotes axonal extension" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 23, no. 9, 5 May 2004 (2004-05-05), pages 1998-2008, XP002334608 ISSN: 0261-4189
- D6: WO 2004/035732 A (FIVE PRIME THERAPEUTICS, INC; WILLIAMS, LEWIS, T; CHU, KETING; LEE, ER) 29 April 2004 (2004-04-29)

**2. NOVELTY and INVENTIVE STEP (Art. 33(2) and (3) PCT)**

2.1 D1 discloses human SMAF-2 (D1, figure 1) which has 100 % identity over 293 amino

acids (full length) with SEQ ID NO: 3 of the application. This document also discloses murine SMAF-2 (SEQ ID NO: 8) , which has 99.31 % identity to murine NsG33 of the present application in 288 amino acids overlap. D1 discloses nucleic acid molecules encoding for said polypeptides, vectors, host cells, antibodies, pharmaceutical compositions. Furthermore, D1 claims the use of SMAF-2 for the treatment of immunological disorders.

- 2.2 As can be seen from the above, document D1 discloses in combination all the features defined in independent claims **1, 22, 51, 56, 73, 74, 89, 108-110**. Hence the subject-matter of these claims is not new (Article 33(2) PCT).
- 2.3 D2 discloses a polypeptide (SEQ ID NO: 1401, pages 3665-3666) which has 100% identity over 293 amino acids with with SEQ ID NO: 3 of the application and a polypeptide (SEQ ID NO: 3369 page 314, GSP:AAM79723) with 98.44 % identity over 128 amino acids with SEQ ID NO: 3. D2 discloses medical uses of said polypeptide, including immune and nervous system disorders (pages 59-61).
- 2.4 D3 discloses a sequence, SEQ ID NO: 675 which has 98.61 % identity ( 98.61 % ungapped) over 216 amino acids (q:s=1-216:46-261) with SEQ ID No: 3 of the application. D3 discloses a polynucleotide, SEQ ID NO: 255, which has 97.19 % identity ( 97.98 % ungapped) over 748 nucleotides (q:s=13-760:36-778) with SEQ ID No: 2. D3 discloses medical uses of said polypeptide, including immune and nervous system disorders (paragraphs [0638-0655]).
- 2.5 D4 discloses SEQ ID NO: 93 and 94 (GENE NO: 21), which have 100 % identity over 103 amino acids (q:s=191-293:1-103) with SEQ ID No: 3 of the present application. SEQ ID NO: 31 of D4 has 100% identity over 421 nucleotides (q:s=688-1108:9-429) with SEQ ID NO: 2 of the application.
- 2.6 D2-D4 disclose all the features defined in independent claims **1, 22, 51, 56, 73, 74, 89, 108-110**. Hence the subject-matter of these claims is not new (Article 33(2) PCT).
- 2.7 Claims **2-21, 23-50, 52-55, 57-72, 75, 76, 90, 91, 104, and 111-121** do not contain any features which, in combination with the features of any claim to which they refer,

meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT) since they refer to embodiments which were disclosed in the prior art cited or represent obvious choices and alternatives for a skilled person in the technical field of the invention.

- 2.7.1 Concerning claims **113-121**, relating to fragments of the human, mouse and/or rat NsG33 polypeptide, comprising the carboxyl-terminal half, the amino-terminal half of NsG33 or missing the signal peptide, are not regarded as inventive since the human, murine and rat NsG33 polypeptides were known in the art (D1-D4) and said fragments do not have any special property or surprising effect which might render them inventive over the prior art. In addition, in view of the lack of any new functional and common structural features, there is no common concept linking each peptide fragment and, should the applicant pursue claims directed to such fragments, non-unity objections in the sense of Rule 13 PCT, might arise in the procedure.
- 2.8 Claims **77-88** and claims **92-103, 105-107** refer to specific uses of the polypeptide of the present invention or related reagents (polynucleotide, vector, host cells, biocompatible cell device or packaging cell line) for the manufacture of a medicament for the treatment of diseases or disorders associated with the nervous system. Although some of the above-mentioned prior art documents disclose general embodiments in the description concerning the use of polypeptides, including that of the present application, for diseases of the nervous system, it appears that said documents do not have sufficient disclosure of the specific use of the NsG33 peptide for treating diseases or disorders associated with the nervous system.
- 2.9 Thus, the combination of the features of claims **77-88, 92-103 and 105-107** does not appear to be known from, or rendered obvious by the available prior art.

### 3. INDUSTRIAL APPLICABILITY (Art. 33(2) and (3) PCT)

- 3.1 For the assessment of the present claims **89-108** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**VI. Certain documents cited**

4. Although D6 does not constitute prior art within the meaning of Rule 64.1(b), it appears to disclose all the features of claims 1-76,89-91,104,108-121. It might therefore be taken into consideration in the regional phase before the EPO. No check has been made as to whether the priority of this application has been validly claimed.

**VIII Certain observations on the international application**

**5. SUFFICIENT DISCLOSURE (Art. 5 PCT)**

- 5.1 The present application provides evidence that the secreted NsG33 polypeptide has an activity as a survival and growth factor for neurons. However, the applicant has not shown that the polypeptide of the invention has any real application in the treatment of a disease, disorder or damage of the nervous system. It appears that the skilled person would have an undue burden in determining, not only which of all the possible peptides claimed (e.g. in claim 1) is useful, but also would have an undue experimental burden to find out which of all the possible diseases named in the application (e.g. in claims 77-88 and 92-103). Thus, the subject-matter of claims 77-88 and 92-103 does not meet the requirements of Article 5 PCT because it lacks sufficient disclosure.

**6. CLARITY (Art. 6 PCT)**

- 6.1 At present, there are too many independent claims and many claims which have

been drafted as separate independent claims, appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought or in respect of the terminology used for the features of that subject-matter. The present set of claims therefore lacks conciseness and as such does not meet the requirements of Article 6 PCT.